IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELI LILLY AND COMPANY and THE TRUSTEES OF PRINCETON UNIVERSITY,	)	
Plaintiffs,	)	
v.	)	C. A. No. _____
TEVA PARENTERAL MEDICINES, INC.,	)	
Defendant.	)	

COMPLAINT

Plaintiffs Eli Lilly and Company and The Trustees of Princeton University (collectively "Plaintiffs"), by their attorneys, for their Complaint, allege as follows:

1. This is an action for patent infringement under the patent laws of the United States, Title 35, United States Code, that arises out of the filing by defendant Teva Parenteral Medicines, Inc. ("Teva") of an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and sell a generic version of ALIMTA® prior to the expiration of U.S. Patent No. 5,344,932.

PARTIES

2. Plaintiff Eli Lilly and Company ("Lilly") is a corporation organized and existing under the laws of the State of Indiana, having its corporate offices and principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285.

3. Plaintiff The Trustees of Princeton University ("Princeton") is a not-for-profit educational institution organized and existing under the laws of the State of New Jersey, having a place of business at One Nassau Hall, Princeton, New Jersey 08540.

4. Upon information and belief, defendant Teva is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 19 Hughes, Irvine, California 92618.

JURISDICTION AND VENUE

5. Jurisdiction and venue are proper in this district pursuant to 28 U.S.C. §§ 1331, 1338(a), 1391, and 1400(b). Teva is subject to personal jurisdiction in Delaware because, among other things, Teva is a resident and citizen of the State of Delaware and has submitted itself to the jurisdiction of courts in Delaware by virtue of its incorporation under Delaware law.

BACKGROUND

6. ALIMTA® is a chemotherapy agent used for the treatment of various types of cancer. ALIMTA® is indicated (in combination with cisplatin) for the treatment of patients with malignant pleural mesothelioma and is also indicated as a single-agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

7. Lilly sells ALIMTA® in the United States pursuant to a New Drug Application that has been approved by the FDA.

COUNT I – U.S. PATENT NO. 5,344,932

8. Plaintiffs incorporate each of the preceding paragraphs 1-7 as if fully set forth herein.

9. United States Patent No. 5,344,932 ("the '932 patent"), entitled "N-(pyrrolo(2,3-d)pyrimidin-3-ylacyl)-Glutamic Acid Derivatives" (Exhibit A hereto), was duly and legally issued on September 6, 1994 to Princeton, as assignee of Edward C. Taylor.

10. Princeton owns the '932 patent. Princeton will be substantially and irreparably damaged by infringement of the '932 patent.

11. Lilly has been granted an exclusive license under the '932 patent. Lilly will be substantially and irreparably damaged by infringement of the '932 patent.

12. ALIMTA® is covered by one or more claims of the '932 patent, and the '932 patent has been listed in connection with that drug product in the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*.

13. By letter dated April 24, 2008 (the "Notice Letter"), Teva notified Lilly and Princeton that Teva had submitted to the FDA an ANDA, No. 90-352, for Teva's Pemetrexed Disodium for Injection, Eq. 500 mg Base/Vial, a drug product that is a generic version of ALIMTA® ("Teva's ANDA Product"). The purpose of the ANDA was to obtain approval under the Federal Food, Drug, and Cosmetic Act ("FDCA") to engage in the commercial manufacture, use, offer for sale, and/or sale of Teva's ANDA Product prior to the expiration of, *inter alia*, the '932 patent.

14. In the Notice Letter, Teva also notified Lilly and Princeton that, as part of its ANDA, Teva had filed certifications of the type described in Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), with respect to, *inter alia*, the '932 patent. Upon information and belief, Teva submitted ANDA No. 90-352 to the FDA containing a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the '932 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, or sale of Teva's ANDA Product.

15. Teva's ANDA Product is covered by one or more claims of the '932 patent.

16. Teva has knowledge of the '932 patent.

17. Teva's filing of ANDA No. 90-352 for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, and/or sale of Teva's ANDA Product before the expiration of the '932 patent is an act of infringement of the '932 patent.

18. The manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Teva's ANDA Product would infringe one or more claims of '932 patent.

19. Upon information and belief, Teva will engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Teva's ANDA Product immediately and imminently upon approval of ANDA No. 90-352.

20. Upon information and belief, use of Teva's ANDA Product in accordance with and as directed by Teva's proposed labeling for that product would infringe one or more claims of the '932 patent.

21. Upon information and belief, Teva will engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Teva's ANDA Product with its proposed labeling immediately and imminently upon approval of ANDA No. 90-352.

22. Upon information and belief, Teva plans and intends to, and will, actively induce infringement of the '932 patent when its ANDA is approved, and plans and intends to, and will, do so immediately and imminently upon approval.

23. Upon information and belief, Teva knows that Teva's ANDA Product and its proposed labeling are especially made or adapted for use in infringing the '932 patent, and that Teva's ANDA Product and its proposed labeling are not suitable for substantial noninfringing use. Upon information and belief, Teva plans and intends to, and will, contribute to infringement of the '932 patent immediately and imminently upon approval of ANDA No. 90-

352.

24. The foregoing actions by Teva constitute and/or will constitute infringement of the '932 patent, active inducement of infringement of the '932 patent, and contribution to the infringement by others of the '932 patent.

25. Upon information and belief, Teva acted without a reasonable basis for believing that it would not be liable for infringing the '932 patent, actively inducing infringement of the '932 patent, and contributing to the infringement by others of the '932 patent.

26. Unless Teva is enjoined from infringing the '932 patent, actively inducing infringement of the '932 patent, and contributing to the infringement by others of the '932 patent, Lilly and Princeton will suffer irreparable injury. Lilly and Princeton have no adequate remedy at law.

WHEREFORE, Plaintiffs request the following relief:

(a) A judgment that Teva has infringed the '932 patent;

(b) A judgment ordering that the effective date of any FDA approval for Teva to make, use, offer for sale, sell, market, distribute, or import Teva's ANDA Product, or any product or compound that infringes the '932 patent, be not earlier than the expiration date of the '932 patent, inclusive of any extension(s) and additional period(s) of exclusivity;

(c) A preliminary and permanent injunction enjoining Teva, and all persons acting in concert with Teva, from making, using, selling, offering for sale, marketing, distributing, or importing Teva's ANDA Product, or any product or compound that infringes the '932 patent, or the inducement of or the contribution to any of the foregoing, prior to the expiration date of the '932 patent, inclusive of any extension(s) and additional period(s) of exclusivity;

(d) A judgment declaring that making, using, selling, offering for sale, marketing, distributing, or importing Teva's ANDA Product, or any product or compound that infringes the '932 patent, prior to the expiration date of the '932 patent, will infringe, actively induce infringement of, and contribute to the infringement by others of the '932 patent;

(e) A declaration that this is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

(f) An award of Plaintiffs' costs and expenses in this action; and

(g) Such further and other relief as this Court may deem just and proper.

Frederick L. Cottrell, III (#2555)
cottrell@rlf.com
Anne Shea Gaza (#4093)
gaza@rlf.com
Richards, Layton & Finger, P.A.
One Rodney Square
920 N. King Street
Wilmington, DE 19801
(302) 651-7700
(302) 651-7701 (Facsimile)

Attorneys for Plaintiffs Eli Lilly and Company and The Trustees of Princeton University

OF COUNSEL:
Bruce R. Genderson
Adam L. Perlman
Ellen E. Oberwetter
Dov P. Grossman
David M. Krinsky
Williams & Connolly LLP
725 Twelfth Street, N.W.
Washington, DC 20005
(202) 434-5000
(202) 434-5029 (Facsimile)

Dated: June 5, 2008

EXHIBIT A

US005344932A

United States Patent [19]

Taylor

[11] Patent Number: 5,344,932

[45] Date of Patent: Sep. 6, 1994

[54] **N-(PYRROLO(2,3-D)PYRIMIDIN-3-YLACYL)-GLUTAMIC ACID DERIVATIVES**

[75] Inventor: **Edward C. Taylor**, Princeton, N.J.

[73] Assignee: **Trustees of Princeton University**, Princeton, N.J.

[21] Appl. No.: **674,541**

[22] Filed: **Mar. 22, 1991**

Related U.S. Application Data

[63] Continuation of Ser. No. 448,742, Dec. 11, 1989, abandoned, and Ser. No. 479,655, Feb. 8, 1990, abandoned.

[51] **Int. Cl.**[5] **C07D 487/04**; A61K 31/505

[52] **U.S. Cl.** **544/280**

[58] **Field of Search** 544/280; 514/258

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,889,859	12/1989	Taylor et al.	514/258
4,996,206	2/1991	Taylor et al.	514/258
4,997,838	3/1991	Akimoto et al.	514/258

FOREIGN PATENT DOCUMENTS

334636	9/1989	European Pat. Off. .

Primary Examiner—Emily Bernhard

Attorney, Agent, or Firm—Mathews, Woodbridge & Collins

[57] **ABSTRACT**

N-(Acyl)glutamic acid derivatives in which the acyl group is substituted with 4-hydroxypyrrolo[2,3-d]-pyrimidin-3-yl group are antineoplastic agents. A typical embodiment is N-[4-(2-{4-hydroxy-6-aminopyrrolo-[2,3-d]pyrimidin-3-yl}ethyl)benzoyl]-L-glutamic acid.

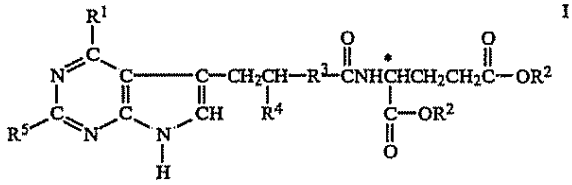
7 Claims, No Drawings

N-(PYRROLO(2,3-D)PYRIMIDIN-3-YLACYL)-GLUTAMIC ACID DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of Ser. No. 07/448,742 filed Dec. 11, 1989 and Ser. No. 07/479,655 filed Feb. 8, 1990 both now abandoned.

The present invention pertains to glutamic acid derivatives having the formula:



I

in which:

R^1 is —OH or —NH_2;

R^2 is hydrogen or a pharmaceutically acceptable cation:

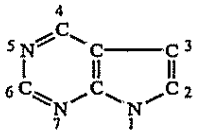
R^3 is 1,4-phenylene or 1,3-phenylene unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl; thienediyl or furanediyl each unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl; cyclohexanediyl; or alkanediyl;

R^4 is hydrogen, methyl, or hydroxymethyl;

R^5 is hydrogen, alkyl of 1 to 6 carbon atoms, or amino; and

the configuration about the carbon atom designated * is S.

The compounds of this invention are herein described as embodying the pyrrolo[2,3-d]pyrimidine heterocyclic ring system which ring system is numbered as follows:



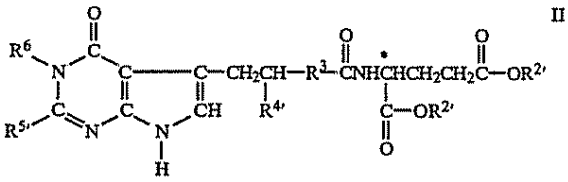
It will be appreciated that the pyrrolo[2,3-d]pyrimidines as depicted by Formula I are the tautomeric equivalent of the corresponding 5-H-6-oxo or 5-H-6-imino structures. Unless otherwise indicated, for simplicity's sake the compounds are depicted herein and named using the 6-hydroxy and 6-amino convention, it being understood the 5-H-6-oxo and 5-H-6-imino structures are fully equivalent.

The compounds of Formula I have an inhibitory effect on one or more enzymes which utilize folic acid, and in particular metabolic derivatives of folic acid, as a substrate. The compounds appear to be particularly active as inhibitors of thymidylate synthetase, which catalyses the methylation of deoxyuridylic acid to deoxythymidylic acid utilizing N^5,N^{10}-methylidenetetrahydrofolate as a coenzyme. The compounds thus can be used, alone or in combination, to inhibit the growth of those neoplasms which otherwise depend upon the inhibited enzyme.

The invention also pertains to the pharmaceutically acceptable salts of the compounds of Formula I, to

processes for the preparation of these compounds and their salts, to chemical intermediates useful in preparation of these compounds, to a method of combatting neoplastic growth in a mammal, and to pharmaceutical compositions containing these compounds or their salts.

A first group of useful chemical intermediates, which can be converted directly to the desired final compounds of Formula I through removal of protecting groups, are compounds of the formula:



II

in which:

R^3 is as defined above;

$R^{2'}$ is hydrogen or a carboxy protecting group;

$R^{4'}$ is hydrogen, methyl, hydroxymethyl, or hydroxymethyl carrying a hydroxy protecting group;

$R^{5'}$ is hydrogen, alkyl, amino, or amino carrying a protecting group; and

R^6 is hydrogen or alkanoyoxy;

at least one of R2',$R^{4'}$, and $R^{5'}$ being a carboxy protecting group, a hydroxy protecting group, or an amino protecting group, respectively.

The compounds of Formula I can be employed in the form of the free dicarboxylic acid, in which case both R^2 groups are hydrogen. Alternatively, the compounds often can be employed advantageously in the form of a pharmaceutically acceptable salt, in which case one or both R^2 groups are a pharmaceutically acceptable cation. Such salt forms, including hydrates thereof, are often crystalline and advantageous for forming solutions or formulating pharmaceutical compositions. Pharmaceutically acceptable salts with bases include those formed from the alkali metals, alkaline earth metals, non-toxic metals, ammonium, and mono-, di- and trisubstituted amines, such as for example the sodium, potassium, lithium, calcium, magnesium, aluminum, zinc, ammonium, trimethylammonium, triethanolammonium, pyridinium, and substituted pyridinium salts. The mono and disodium salts, particularly the disodium salt, are advantageous.

The group R^3 is a divalent group having at least two carbon atoms between the carbon atoms carrying the free valence bonds. R^3 for example can be a 1,4-phenylene or 1,3-phenylene ring which is unsubstituted or optionally substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl.

Alternatively, R^3 can be a thienediyl or furanediyl group, that is, a thiophene or furane ring from which two hydrogen atoms have been removed from two ring carbon atoms, as for example the thiene-2,5-diyl, thiene-3,5-diyl, thiene-2,4-diyl, and thiene-3,4-diyl ring systems and the the furane-2,5-diyl, furane-3,5-diyl, furane-2,4-diyl, and furane-3,4-diyl ring systems, which ring systems can be unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl. It will be appreciated that whereas in the abstract the thiene-3,5-diyl system is the equivalent of the thiene-2,4-diyl system, the two terms are utilized herein to denote the two isomeric forms resulting from the orientation of the thiophene ring within the remainder of the molecule:

e.g. the structure in which the depicted carboxy group adjacent to R^3 is in the 2-position of the thiophene ring and that in which the depicted carboxy group adjacent to R^3 is in the 3-position of the thiophene ring. The same conventionas apply to the furane ring.

Alternatively, R^3 can be a cyclohexanediyl group, namely a divalent cycloalkane group of 6 carbon atoms such as cyclohexane-1,3-diyl and cyclohexane-1,4-diyl.

Alternatively, R^3 can be a alkanediyl, namely a straight or branched divalent aliphatic group of from 2 to 4 carbon atoms such as ethano, trimethylene, tetramethylene, propane-1,2-diyl, propane-2,3-diyl, butane-2,3-diyl, butane-1,3-diyl, and butane-2,4-diyl. It again will be appreciated that whereas in the abstract propane-1,2-diyl is the equivalent of propane-2,3-diyl, and butane-1,3-diyl the equivalent of butane-2,4-diyl, the two terms are utilized herein to denote the two isomeric forms resulting from the orientation of an unsymmetrical alkanediyl chain with respect to the remainder of the molecule.

The protecting groups designated by $R^{2'}$, $R^{4'}$ and $R^{5'}$ and utilized herein denote groups which generally are not found in the final therapeutic compounds but which are intentionally introduced at a stage of the synthesis in order to protect groups which otherwise might react in the course of chemical manipulations, thereafter being removed at a later stage of the synthesis. Since compounds bearing such protecting groups thus are of importance primarily as chemical intermediates (although some derivatives also exhibit biological activity), their precise structure is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973; Greene, Th. W. "Protective Groups in Organic Synthesis", Wiley, New York, 1981; "The Peptides", Vol. I, Schröder and Lubke, Academic Press, London and New York, 1965; "Methoden der organischen Chemie", Houben-Weyl, 4th Edition, Vol.15/I, Georg Thieme Verlag, Stuttgart 1974, the disclosures of which are incorporated herein by reference.

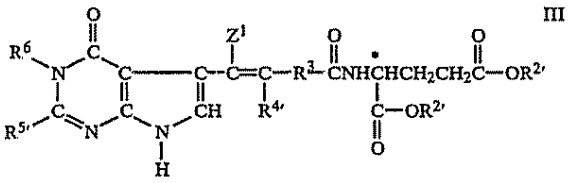
With respect to $R^{2'}$, a carboxy group can be protected as an ester group which is selectively removable under sufficiently mild conditions not to disrupt the desired structure of the molecule, especially a lower alkyl ester of 1 to 12 carbon atoms such as methyl or ethyl and particularly one which is branched at the 1-position such as t.-butyl; and such lower alkyl ester substituted in the 1- or 2-position with (i) lower alkoxy, such as for example, methoxymethyl, 1-methoxyethyl, and ethoxymethyl, (ii) lower alkylthio, such as for example methylthiomethyl and 1-ethylthioethyl; (iii) halogen, such as 2,2,2-trichloroethyl, 2-bromoethyl, and 2-iodoethoxycarbonyl; (iv) one or two phenyl groups each of which can be unsubstituted or mono-, di- or tri-substituted with, for example lower alkyl such as tert.-butyl, lower alkoxy such as methoxy, hydroxy, halo such as chloro, and nitro, such as for example, benzyl, 4-nitrobenzyl, diphenylmethyl, di-(4-methoxyphenyl)methyl; or (v) aroyl, such as phenacyl. A carboxy group also can be protected in the form of an organic silyl group such as trimethylsilylethyl or tri-lower alkylsilyl, as for example trimethylsilyloxycarbonyl.

With respect to $R^{4'}$, a hydroxy group can be protected through the formation of acetals and ketals, as for example through formation of the tetrahydropyr-2-yloxy (THP) derivative.

With respect to $R^{5'}$, an amino group can be protected as an amide utilizing an acyl group which is selectively removable under mild conditions, especially formyl, a lower alkanoyl group which is branched α to the carbonyl group, particularly tertiary alkanoyl such as pivaloyl, or a lower alkanoyl group which is substituted in the position α to the carbonyl group, as for example trifluoroacetyl.

Preferred compounds of Formula I are those wherein R^5 is amino or hydrogen. Within this class, R^1 preferably is hydroxy, R^3 is 1,4-phenylene, and R^4 is hydrogen or hydroxymethyl. Also preferred within this class are the compounds in which R^1 is hydroxy, R^3 is thienediyl, and R^4 is hydrogen or hydroxymethyl.

The compounds of this invention can be prepared according to a first process through catalytic hydrogenation of a compound of the formula:



III

in which:

Z^1 is hydrogen, or Z^1 taken together with $R^{4'}$ is a carbon-carbon bond;

$R^{2'}$ is hydrogen or a carboxy protecting group;

R^3 and R^6 are as defined above;

$R^{4'}$, when taken independently of Z^1, is hydrogen, methyl, hydroxymethyl, or hydroxymethyl substituted with a hydroxy protecting group; and

$R^{5'}$ is hydrogen, alkyl of 1 to 6 carbon atoms, amino, or an amino protecting group.

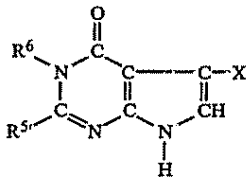
Suitable hydrogenation catalysts include noble metals and noble metal oxides such as palladium or platinum oxide, rhodium oxide, and the foregoing on a support such as carbon or calcium oxide.

When in Formula III, Z^1 taken together with $R^{4'}$ is a carbon-carbon bond, that is, when a triple bond is present between the two carbon atoms to which Z^1 and $R^{4'}$ are bound, $R^{4'}$ in the hydrogenation product will be hydrogen. Absent any chirality in R^3 (or any protecting group encompassed by $R^{2'}$, $R^{4'}$ and/or $R^{5'}$), the hydrogenation product will be a single enantiomer having the S-configuration about the carbon atom designated *. This also is true when Z^1 and $R^{4'}$ are each hydrogen, that is, when a double bond is present between the two carbon atoms to which Z^1 and $R^{4'}$ are bound.

When, on the other hand, $R^{4'}$ is other than hydrogen, a mixture of the R,S and S,S diastereomers is obtained. The diastereomeric mixture can be used therapeutically as such (after removal of the protecting groups) or can be separated mechanically as by chromatography. Alternatively, the individual diastereomers can be separated chemically by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, campboric acid, alphabromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the individual diastereomeric bases, optionally repeating the process, so as obtain either or both substantially free of the other; i.e., in a form having an optical purity of >95%.

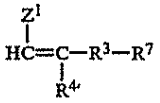
The protecting groups encompassed by $R^{2'}$, $R^{4'}$, $R^{5'}$, and/or R^6 can be removed following hydrogenation through acidic or basic hydrolysis, as for example with hydrogen chloride to cleave an $R^{4'}$ protecting group or with sodium hydroxide to cleave $R^{2'}$ or $R^{5'}$ protecting groups, thereby yielding the compounds of Formula I. Methods of removing the various protective groups are described in the standard references noted above and incorporated herein by reference.

Compounds of Formula III can be prepared utilizing procedures analogous to those described in U.S. Pat. No. 4,818,819, utilizing however the corresponding halogenated pyrrolo[2,3-d]pyrimidine. Thus a pyrrolo[2,3-d]pyrimidine of the formula:



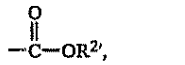
IV

in which X is bromo or iodo, $R^{5'}$, and R^6 are as herein defined, is allowed to react with an unsaturated compound of the formula:

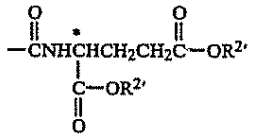


V

in which Z^1, R^3 and $R^{4'}$ are as herein defined, and R^7 is



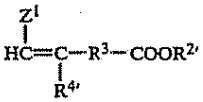
or



in which $R^{2'}$ is as herein defined, in the presence of a palladium/trisubstituted phosphine catalyst of the type described in U.S. Pat. No. 4,818,819, the disclosure of which is incorporated herein by reference.

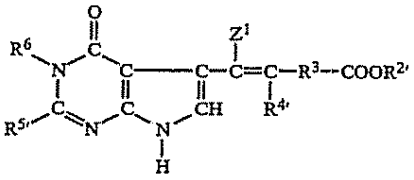
When R^7 is $-CONHCH(COOR^{2'})CH_2CH_2COOR^{2'}$, the product of this coupling reaction is hydrogenated, and any protecting group removed, as described above.

Alternatively, a compound of Formula IV is allowed to react with a compound of the formula:



VI

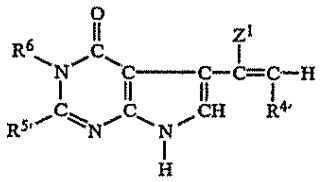
in which Z^1, $R^{2'}$, R^3, and $R^{4'}$ are as herein defined in the presence of a palladium/trisubstituted phosphine catalyst of the type described in U.S. Pat. No. 4,818,819 to yield an intermediate of the formula:



VII

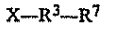
The product of Formula VII then can be hydrogenated, hydrolysed to remove the $R^{2'}$ and R^6 protecting groups, and, optionally with intermediate protection of any amino group encompassed by $R^{5'}$, and coupled with a protected glutamic acid derivative in the manner described in U.S. Pat. No. 4,684,653 using conventional condensation techniques for forming peptide bonds such as DCC or diphenylchlorophosphonate, following which the protecting groups are removed.

In a further variant, compounds of Formula III can be prepared utilizing the procedures described in U.S. Pat. No. 4,818,819. Thus a compound of the formula:



VIII

in which Z^1, $R^{4'}$, $R^{5'}$, and R^6 are as herein defined, is allowed to react with a compound of the formula:



IX

in which X, R^3, and R^7 are as herein defined, in the presence of a palladium/trisubstituted phosphine catalyst of the type described in U.S. Pat. No. 4,818,819. This variant of the process is particularly suitable for, but is not limited to, preparation of those compounds in which R^4 is hydroxymethyl, in which case $R^{4'}$ in Formula VI is a protected hydroxymethyl group, as for example tetrahydropyran-2-yloxymethyl.

Compounds of Formula VIII also can be obtained by the methods of U.S. Pat. No. 4,818,819 by treating a compound of Formula IV with an unsaturated compound of the formula:

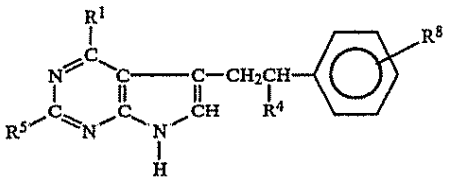
X

in which $R^{4''}$ is methyl, a protected hydroxymethyl, or a trisubstituted silyl group in the presence of a palladium/trisubstituted phosphine catalyst of the type discussed above. This procedure is particularly suitable for, but is not limited to, preparation of those compounds in which R^4 is hydroxymethyl.

Although not always the case, the compounds of Formula IV in which R^6 is hydrogen can tend to be somewhat insoluble in solvents suitable for the reaction described in U.S. Pat. No. 4,818,819. In such instances, the compounds of Formula IV in which R^6 is hydrogen can be first treated with with sodium hydride and a suitable alkyl alkanoate (such as chloromethyl pivalate) to introduce an alkanoyloxy group in the 5-position and increase solubility.

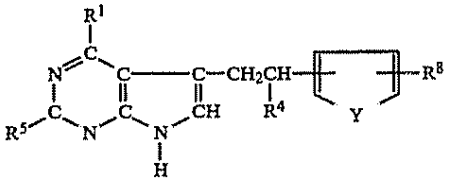
A useful subclass of compounds useful both as intermediates and for their effect on enzymes are derivatives

of Formula XI and XII lacking the glutamic acid side-chain:



XI

and



XII

in which:

R^1 is —OH or —NH_2;

R^4 is hydrogen, methyl, or hydroxymethyl;

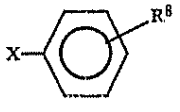
R^5 is hydrogen, alkyl of 1 to 6 carbon atoms, or amino;

R^8 is hydrogen, chloro, fluoro, methyl, methoxy, trifluoromethyl, or carboxy; and

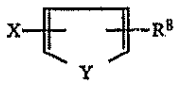
Y is —S— or —O—; and

the pharmaceutically acceptable salts thereof.

Compounds of Formulas XI and XII are obtained by allowing a compound of Formula VII to react with a compound of the formula:

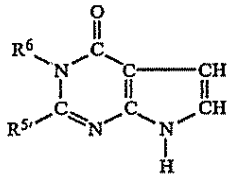


or



in which X, Y, and R^8 are as herein defined, by the methods of U.S. Pat. No. 4,818,819, namely in the presence of a palladium/trisubstituted phosphine catalyst, with the resulting coupled product being hydrogenated and hydrolysed to remove the $R^{2'}$ protecting group. Typical compounds of Formulas XI and XII are 3-(2-phenylethyl)-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(4-carboxyphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]-pyrimidine, 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-(2-phenylethyl)-4-hydroxypyrrolo[2,3-d]pyrimidine, 3-(2-phenylethyl)-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-(2-phenyl-3-hydroxypropyl)-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(thien-2-yl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(thien-2-yl)ethyl]-4-hydroxypyrrolo[2,3-d]pyrimidine, 3-[2 -(thien-2-yl)ethyl]-4-hydroxy-6-methylpyrrolo[2,3-d]-pyrimidine, 3-[2-(thien-3-yl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(thien-3-yl)ethyl]-4-hydroxypyrrolo[2,3-d]pyrimidine, 3-[2-(thien-3-yl)ethyl]-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-[2-(fur-2-yl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(fur-2-yl)ethyl]-4-hydroxypyrrolo[2,3-d]pyrimidine, 3-[2-(fur-2-yl)ethyl]-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-[2-(fur-3-yl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(fur-3-yl)ethyl]-4-hydroxypyrrolo[2,3-d]pyrimidine, and 3-[2-(fur-3-yl)ethyl]-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine.

As discussed above, the compounds of this invention can be prepared utilizing the palladium catalyzed coupling of various unsaturated compounds described in U.S. Pat. No. 4,818,819 and the glutamic acid coupling reactions described in U.S. Pat. No. 4,684,653, substituting the appropriate pyrrolo[2,3-d]pyrimidine for the pyrido[2,3-d]pyrimidine therein disclosed. The pyrrolo[2,3-d]pyrimidine intermediates of Formula IV above can be obtained by treating a compound of the formula:



XIII

in which $R^{5'}$ and R^6 are as herein defined with N-iodosuccinimide to yield the corresponding 2,3-diiodopyrrolo[2,3-d]pyrimidine which then is treated with zinc and acetic acid to remove selectively the iodine atom in the 2-position, yielding the corresponding 3-iodopyrrolo[2,3-d]pyrimidine of Formula IV.

According to the foregoing processes, compounds of Formula II in which R^1 is —OH are obtained. When a compound of Formula I in which R^1 is —NH_2 is desired, a compound in which R^1 is —OH can be treated with 1,2,4-triazole and (4-chlorophenyl)dichlorophosphate and the product of this reaction then treated with concentrated ammonia.

As noted, the compounds of this invention have an effect on one or more enzymes which utilize folic acid, and in particular metabolic derivatives of folic acid, as a substrate. For example, N-(4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl)-L-glutamic acid demonstrates potent inhibitory effects against growth of human T-cell derived lyphoblastic leukemia cells (CCRF-CEM), exhibiting an IC_{50} of 0.004 μ/ml. Cytotoxicity is not reversed by addition of purines such as hypoxanthine or by addition of aminoimidazolecarboxamide but is reversed by addition of thymidine, indicating specific inhibition in the tymidylate cycle and not in de novo purine synthesis. The compounds can be used, under the supervision of qualified professionals, to inhibit the growth of neoplasms including choriocarcinoma, leukemia, adenocarcinoma of the female breast, epidermid cancers of the head and neck, squamous or small-cell lung cancer, and various lymphosarcomas. The compounds can also be used to treat mycosis fungoides and psoriasis.

The compounds can be administered orally but preferably are administered parenterally, alone or in combination with other therapeutic agents including other anti-neoplastic agents, steroids, etc., to a mammal suffering from neoplasm and in need of treatment. Paren-

teral routes of administration include intramuscular, intrathecal, intravenous and intra-arterial. Dosage regimens must be titrated to the particular neoplasm, the condition of the patient, and the response but generally doses will be from about 10 to about 100 mg/day for 5–10 days or single daily administration of 250–500 mg, repeated periodically; e.g. every 14 days. While having a low toxicity as compared to other antimetabolites now in use, a toxic response often can be eliminated by either or both of reducing the daily dosage or administering the compound on alternative days or at longer intervals such as every three days. Oral dosage forms include tablets and capsules containing from 1–10 mg of drug per unit dosage. Isotonic saline solutions containing 20–100 mg/ml can be used for parenteral administration.

The following examples will serve to further illustrate the invention. In the NMR data, "s" denotes singlet, "d" denotes doublet, "t" denotes triplet, "q" denotes quartet, "m" denotes multiplet, and "br" denotes a broad peak.

EXAMPLE 1

3-Iodo-4-hydroxy-6-Pivaloylaminopyrrolo[2,3-d]pyrimidine

A mixture of 3.0 g (0.02 mole) of 4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine and 8.4 g (0.07 mol) of pivaloyl chloride in 40 mL of pyridine is stirred for 30 minutes at from 80° to 90° C., the mixture then evaporated to dryness, and the residue dissolved in 30 mL of methanol. Addition of 10% aqueous ammonia yields 4.2 g (89%) of 4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which can be further purified by chromatography through silica gel, eluting with 8% methanol in methylene chloride. mp 295° C. ^{1}NMR (d_6-DMSO)δ1.20(s, 9H) , 6.37 (d, J=3.4 Hz, 1H), 6.92 (d, J=3.4 Hz, 1H), 10.78 (s, 1H), 11.56 (s, 1H), 11.82 (s, 1H). Anal. Calc. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.16; H, 6.01; N, 23.67.

To a mixture of 4.7 g (20 mmol) of 4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine in 200 mL of dimethylformamide are added 9.9 g (44 mmol) of N-iodosuccinamide. The mixture is stirred at ambient temperature in the dark for 18 hours. Most of the dimethylformamide is removed by evaporation and the residual slurry poured into 300 mL of water. The resulting solid is collected by filtration and dried under vacuum over phosphorus pentoxide to yield 2,3-diiodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which can be purified further by chromatography over silica eluting with 2.5% methanol in methylene chloride. mp >290° C. ^{1}NMR (d_6-DMSO)δ1.18(s, 9H), 10.85 (s, 1H), 11.85 (s, 1H), 12.42 (s, 1H). Anal. Calc. for $C_{11}H_{12}N_4O_2I_2$: C, 27.18; H 2.49; N, 11.53; I, 52.22. Found: C, 27.51; H, 2.51; N, 11.27;I, 52.02.

In a similar fashion but starting with 4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine and 4-hydroxypyrrolo[2,3-d]pyrimidine (7-deazahypoxanthine) there are respectively obtained 2,3-diiodo-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, mp 233° C., and 2,3-diiodo-4-hydroxypyrrolo[2,3-d]pyrimidine, mp >205° C. (compound loses iodine). ^{1}NMR (d_6-DMSO)δ7.79 (s, 1H), 11.93 (s, 1H), 12.74 (s, 1H).

To a mixture of 4.86 g of 2,3-diiodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine in 100 mL of glacial acetic acid and 25 mL of water are added 1.3 g (20 mmol) of zinc powder. The mixture is stirred at ambient temperature for 18 hours, diluted with 500 mL of water, and cooled. The solid is collected through filtration and dried under vacuum over phosphorus pentoxide to yield 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which can be purified further by chromatography over silica eluting with 2.5% methanol in methylene chloride. mp >240° C. ^{1}NMR (d_6-DMSO)δ1.20(s, 9H), 7.12 (d, J=1.8 Hz, 1 H), 10.82 (s, 1H), 11.79 (s, 1H), 11.89 (s, 1H). Anal. Calc. for $C_{11}H_{13}N_4O_2I$: C, 36.69; H 3.64; N, 15.56; I, 35.24. Found: C, 36.91; H, 3.58; N, 15.65; I, 35.56.

In a similar fashion from 2,3-diiodo-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine and 2,3-diiodo-4-hydroxypyrrolo[2,3-d]pyrimidine, there are respectively obtained 3-iodo-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine m.p 245° C., and 3-iodo-4-hydroxypyrrolo[2,3-d]pyrimidine, mp >245° C. (compound loses iodine). ^{1}NMR (d_6-DMSO)δ7.20 (d, J=2.2 Hz, 1H), 7.82 (d, J=2.8 Hz, 1H), 11.85 (d, J=1.1 Hz, 1H), 12.17 (s, 1H).

EXAMPLE 2

Dimethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate

To a mixture of 3.6 g (10 mmol) of well-dried 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine in 40 mL of dimethylformamide are added 4.0 g (13.19 mmol) of dimethyl N-(4-ethynylbenzoyl)-L-glutamate, 0.38 g of copper (I) iodide, 3 mL of triethylamine, and 1.0 g of tetrakis-(triphenylphosphine)palladium. This mixture is stirred at ambient temperatures for two hours and then poured into 500 mL of water. The solid is collected by filtration, air dried, and then refluxed in 200 mL of methanol. The mixture is cooled and the solid collected by filtration, dissolved in two liters of 10% methanol in methylene chloride, and chromatographed over silica. Initial black bands are rechromatographed and the combined colorless bands from the first and second runs are evaporated to give 3.5 g of dimethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate which can be purified further by recrystallization from 50% methanol in methylene chloride. mp 280°–285° C. ^{1}NMR (d_6-DMSO)δ1.21 (s, 9H), 1.96–2.15 (m, 2H), 2.44 (t, J=7.5 Hz, 2H) 3.56 (s, 3H), 3.62 (s, 3H), 4.40–4.45 (m, 1H), 7.43 (s, 1H), 7.53 (d, J=8.4 Hz, 2 H), 7.87 (d, J=8.4 Hz, 2 H), 8.82 (d, J=7.4 Hz, 1 H), 10.95 (s, 1H), 11.95 (s, 1H). Anal. Calc. for $C_{27}H_{29}N_5O_7$: C, 60.56; H 5.46; N, 13.08. Found: C, 60.55; H, 5.46; N, 12.89.

In a similar fashion by substituting an equivalent amount of dimethyl N-(pent-4-ynoyl)-L-glutamate, dimethyl N-(hept-6-enoyl)-L-glutamate, and dimethyl N-(hex-5-ynoyl)-L-glutamate for dimethyl N-(4-ethynylbenzoyl)glutamate in the foregoing procedure, there are obtained dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)pent-4-ynoyl]-L-glutamate, dimethyl N-[7-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]-pyrimidin-3-yl)hept-6-enoyl]-L-glutamate, and dimethyl N-[6-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hex-5-ynoyl]-L-glutamate.

Dimethyl N-(hex-5-ynoyl)-L-glutamate can be obtained in the manner described generally in U.S. Pat. No. 4,882,334 issued Nov. 21, 1989, the disclosure of which is incorporated herein by reference, by allowing hex-5-ynoic acid chloride (obtained by treating hex-5-ynoic acid with thionyl chloride) to react with dimethyl

L-glutamate in the presence of an acid acceptor such as triethylamine. Hex-5-ynoic acid in turn can be prepared, for example, by alkaline hydrolysis of 5-cyanopent-1-yne.

EXAMPLE 3

Diethyl N-[4-{1-hydroxy-3-(4-hydroxy-06-aminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl}benzoyl]glutamate

A mixture of 14.6 g of 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 7.6 g of 2-(2-propynyloxy)-tetrahydropyran, 798 mg (10%) of palladium chloride, 2.36 g (20%) of triphenyl phosphine, 428 mg (5%) of cuprous iodide, 45 ml of triethyl amine and 700 ml of acetonitrile is heated at reflux under nitrogen for 12 hours. There then are added to the hot reaction mixture 3.2 g of 2-(2-propynyloxy)-tetrahydropyran and reflux is continued for an additional 12 hours. After heating for a total of 24 hours under reflux, the solvent is removed under reduced pressure, and the residue filtered through silica gel using 2% methanol in methylene chloride. This filtrate is concentrated and chromatographed on silica gel eluting with 20:1 ethyl acetate:hexane mixture to give 3-(3-tetrahydropyr-2-yloxy-prop-1-yn-1-yl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which is further purified by recrystallization with ethyl acetate.

A mixture of 2 g of 3-(3-tetrahydropyr-2-yloxyprop-1-yn-1-yl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 40 ml of methanol, 20 ml of chloroform, 40 mg of 5% palladium on barium sulfate, and 40 mg of synthetic quinoline is stirred under 1 atmosphere hydrogen pressure for 40 min. The solvent then is removed by evaporation and the residue diluted with methylene chloride. The methylene chloride solution is filtered through silica gel with 2% methanol in methylene chloride to remove catalyst and the filtrate then concentrated to give an oil which upon adding ether yields 3-(3-tetrahydropyr-2-yloxyprop-1-en-1-yl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which can be further purified through column chromatography eluting with ethyl acetate and recrystallization using ethyl acetate.

A mixture containing 3.48 g of 3-(3-tetrahydropyr-2-yloxyprop-1-en-1-yl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3.12g (1.2 equiv.) of diethyl N-(4-iodobenzoyl)glutamate, 546 mg (20%) of tris-(2-methylphenyl)phosphine, 201 mg (10%) of palladium acetate and 85.5 mg (5%) of cuprous iodide in 15 ml of triethylamine and 240 ml of acetonitrile is heated at reflux under nitrogen. After 12 hours., 1.17 g of diethyl N-(4-iodobenzoyl)glutamate are added and the reaction mixture is heated at reflux under nitrogen for an additional 12 hours. The reaction mixture then is concentrated under reduced pressure and the residue chromatographed on silica gel, eluting with 20:1 ethyl acetate:-hexane. (Any recovered starting material can be recycled through the foregoing procedure.) The concentrated material is dissolved in 1:5 ethyl acetate:ether and this solution is refrigerated for 15 hours. The solid which forms is collected by filtration, washed with cold ethyl acetate and dried to yield diethyl N-[4-(1-(tetrahydropyr-2-yloxy)-3-(4-hydroxy-6 -pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-en-2yl)benzoyl]glutamate.

EXAMPLE 4

Dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl}ethynyl)thien-2-ylcarbonyl]-L-glutamate

A mixture of 2.0 g of 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 1.2 g. of trimethylsilylacetylene, 0.1 g of palladium chloride, 0.23 g of triphenylphosphine, 0.06 g of cuprous iodide, and 2.6 g of triethylamine in 100 mL of acetonitrile is heated in a sealed tube for 1.5 hours at 50° C. and then at reflux for 3 hours. The solvent is removed under reduced pressure and the residue triturated with 1:1 ethyl acetate:hexanes and filtered. The solid thus collected is dissolved in methylene chloride and this solution is passed through a pad of silica gel eluting with 1% methanol on methylene chloride. The eluate is concentrated to yield 3-trimethylsilylethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine.

To a solution of 1.5 g of 3-trimethylsilylethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine in 100 mL of anhydrous tetrahydrofuran cooled to 0° C. are added under nitrogen 4.75 mL of 1M tetrabutylammonium fluoride in anhydrous tetrahydrofuran. After 5 minutes, the reaction mixture is allowed to attain room temperature and is then stirred for 2 hours. The solvent is removed under reduced pressure and the residue purified by chromatography over silica gel to yield 3-ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine.

A mixture of 1.70 g. of 3-ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 2.30 g. of dimethyl N-(5-bromothien-2-ylcarbonyl)-L-glutamate (prepared as described in U.S. Pat. No. 4,882,333 issued Nov. 21, 1989, the disclosure of which is incorporated herein by reference), 44 mg. of palladium chloride, 130 mg. of triphenylphosphine, 25 mg. of cuprous iodide, and 1.13 mL. of triethylamine in 30 mL. of acetonitrile is heated at reflux for 3 hours and then cooled to ambient temperature. The solvent is removed under reduced pressure and the residue column chromatographed (Waters 500) eluting with 1:19 methanol:methylene chloride to yield dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethynyl)thien-2-ylcarbonyl]-L-glutamate.

By substituting equivalent amounts of diethyl N-(4-bromothien-2-ylcarbony)-L-glutamate, and diethyl N-(5-bromothien-3-ylcarbony)-L-glutamate in the foregoing procedure, there are respectively obtained diethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)thien-2-ylcarbonyl]-L-glutamate and diethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin3-ylethynyl)thien-3-ylcarbonyl]-L-glutamate.

Diethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)fur-2-ylcarbonyl]-L-glutamate and diethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)fur-3-ylcarbonyl]-L-glutamate can be similarly obtained from diethyl N(4-bromofur-2-ylcarbony)-L-glutamate and diethyl N-(5-bromofur-3-ylcarbony)-L-glutamate, respectively.

Similarly from dimethyl N-(2-fluoro-4-iodobenzoyl)-L-glutamate and dimethyl N-(3-fluoro-4-iodobenzoyl)-L-glutamate (prepared as described in U.S. Pat. No. 4,889,859 issued Dec. 26, 1989, the disclosure of which is incorporated herein by reference), there are respec-

tively obtained dimethyl N-[2-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate and dimethyl N-[3-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate.

EXAMPLE 5

Dimethyl N-[4-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-ylethynyl)-benzoyl]-L-glutamate

By allowing 3-iodo-4-hydroxypyrrolo[2,3-d]pyrimidine to react with dimethyl N-(4-ethynylbenzoyl)-L-glutamate in the manner described in Example 2, there is obtained dimethyl N-[4-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate which is purified by chromatography over silica, m.p. 160 ° C. (dec.). ^{1}NMR (d_6-DMSO)δ1.98–2.15 (m, 2H), 2.45 (t, J=7.5 Hz, 2H) 3.57 (s, 3H), 3.64 (s, 3H), 4.40–4.45 (m, 1H), 7.51 ((d, J=2.5 Hz, 1H), 7.55 (d, J=8.2 Hz, 2 H), 7.87 (s, 1H), 7.90 (d, J=8.2 Hz, 1 H), 11.97 ((d, J=3.7 Hz, 1 H), 12.31 (s, 1H).

Alternatively, by substituting equivalent amounts of methyl 4-ethynylbenzoate, 4-ethynyltoluene, 4-ethynylbenzene, 4-ethynylchlorobenzene, 4-ethynylfluorobenzene, 3-ethynylfluorobenzene, and 1-methoxy-4ethynylbenzene in the procedure of Example 2, there are obtained methyl 4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate, 3-(4-methylphenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3-phenylethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3-(4-chlorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3-(4 -fluorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3-(3-fluorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, and 3-(4-methoxyphenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine.

Use of 3-iodo-4-hydroxypyrrolo[2,3-d]pyrimidine in place of 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine with methyl 4-ethynylbenzoate, 4-ethynyltoluene, 4-ethynylbenzene, 4-ethynylchlorobenzene, 4-ethynylfluorobenzene, 3-ethynylfluorobenzene, and 1-methoxy-4-ethynylbenzene yields respectively methyl 4-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate, 3-(4-methylphenyl)ethynyl-4-hydroxypyrrolo[2,3-d]pyrimidine, 3-phenylethynyl-4-hydroxypyrrolo[2,3-d]pyrimidine, 3-(4-chlorophenyl)ethynyl-4-hydroxypyrrolo[2,3-d]pyrimidine, 3-(4-fluorophenyl-)ethynyl-4-hydroxypyrrolo[2,3-d]pyrimidine, and 3-(4-methoxyphenyl)ethynyl4-hydroxypyrrolo[2,3-d]pyrimidine.

Ten grams of 3-iodo-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine are allowed to react with 2.19 g of 80% sodium hydride oil dispersion and 75 ml of dimethylformamide with the exclusion of moisture. After 30 minutes, 6.02 g of chloromethyl pivalate are added. This mixture is stirred for three hours poured into water, and neutralized with acetic acid. The solid is chromatographed on silica gel with acetone-dichloromethane to yield 3-iodo-4-hydroxy-l,5-bis-(pivaloyloxy)-6-methylpyrrolo[2,3-d]pyrimidine, m.p. 155° C. initially, followed by 3-iodo-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, m.p. 236° C.

Use of 3-iodo-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine in the procedure of Example 2 then yields dimethyl N-[4-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate, m.p. 196° C. Anal. Calc. for $C_{29}H_{32}N_4O_8$: C, 61.70; H 5.71; N, 9.92. Found: C, 61.90; H, 5.71; N, 9.95.

Use of 3-iodo-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine in place of 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine with methyl 4-ethynylbenzoate, 4-ethynyltoluene, 4-ethynylbenzene, 4-ethynylchlorobenzene, 4-ethynylfluorobenzene, 3-ethynylfluorobenzene, and 1-methoxy-4-ethynylbenzene yields methyl 4-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate, 3-(4-methylphenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]-pyrimidine, 3-phenylethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-(4-chlorophenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-(4-fluorophenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, and 3-(4-methoxyphenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine.

EXAMPLE 6

Dimethyl N-{4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamate

A mixture of 1.0 g of dimethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate in 250 mL of 50% methanol in methylene chloride and 0.8 g of 3% palladium-on-carbon is hydrogenated at 50 p.s.i. for three hours, filtered, and concentrated under reduced pressure. The solid is collected by filtration and dried to yield 0.72 g of dimethyl N-{4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamate- mp 247° C. ^{1}NMR (d_6-DMSO)δ1.21 (s, 9H), 1.90–2.12 (m, 2H), 2.42 (t, J=7.4 Hz, 2H), 2.92 (t, J=4 Hz, 2H), 2.97 (t, J=4 Hz, 2H), 3.55 (s, 3H), 3.61 (s, 3H), 4.38–4.45 (m, 1H), 6.61 (s, 1H), 7.27 (d, J=8.2 Hz, 2 H), 7.75 (d, J=8.2 Hz, 2 H), 8.64 (d, J=7.4 Hz, 1 H), 10.75 (s, 1H), 11.22 (s, 1H) . Anal. Calc. for $C_{27}H_{33}N_5O_7$: C, 60.10; H 6.17; N, 12 . 98. Found: C, 59.94; H, 6.15; N, 12.72 .

EXAMPLE 7

Dimethyl N-{5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcarbonyl}-L-glutamate

By subjecting dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethynyl)thien-2-ylcarbonyl]-L-glutamate to the hydrogenation procedure of Example 6, there is obtained dimethyl N-{5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)-ethyl]thien-2-ylcarbonyl}-L-glutamate.

Similarly the following compounds are subjected to the hydrogenation of Example 6:

(a) dimethyl N-[2-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate;

(b) dimethyl N-[3-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)-benzoyl]-L-glutamate;

(c) diethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)thien-2-ylcarbonyl]-L-glutamate;

(d) diethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)thien-3-ylcarbonyl]-L-glutamate;
(e) dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)pent-4-ynoyl]-L-glutamate;
(f) dimethyl N-[7-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hept-6-enoyl]-L-glutamate;
(g) dimethyl N-[6-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hex-5-ynoyl]-L-glutamate;
(h) methyl 4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate;
(i) 3-(4-methylphenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(j) 3-phenylethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(k) 3-(4-chlorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(l) 3-(4-fluorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(m) 3-(3-fluorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(n) 3-(4-methoxyphenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(o) methyl 4-(4-hydroxy-5-pivaloyloxy-6-methyl-pyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate;
(p) 3-(4-methylphenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
(q) 3-phenylethynyl-4-hydroxy-5-pivaloyloxy-6methyl-pyrrolo[2,3-d]pyrimidine;
(r) 3-(4-chlorophenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
(s) 3-(4-fluorophenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
(t) 3-(4-methoxyphenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
(u) methyl 4-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate;
(v) 3-(4-methylphenyl)ethynyl-4-hydroxypyrrolo2,3-d]pyrimidine;
(w) 3-phenylethynyl-4-hydroxypyrrolo[2,3-d]pyrimidine;
(x) 3-(4-chlorophenyl)ethynyl-4-hydroxypyrrolo2,3-d]pyrimidine;
(y) 3-(4-fluorophenyl)ethynyl-4-hydroxypyrrolo2,3-d]pyrimidine; and
(z) 3-(4-methoxyphenyl)ethynyl-4-hydroxypyrrolo[2,3-d]pyrimidine.

There are respectively obtained:

(a) dimethyl N-[2-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethyl)benzoyl]-L-glutamate;
(b) dimethyl N-[3-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethyl)benzoyl]-L-glutamate;
(c) diethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethyl)thien-2-ylcarbonyl]-L-glutamate;
(d) diethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethyl)thien-3-ylcarbonyl]-L-glutamate;
(e) dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)pentyl]-L-glutamate;
(f) dimethyl N-[7-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)heptyl]-L-glutamate;
(g) dimethyl N-[6-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hexyl]-L-glutamate;
(h) methyl 4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoate;
(i) 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(j) 3-(2-phenylethyl)-4-hydroxy-6-pivaloylaminopyrrolo [2,3-d]pyrimidine;
(k) 3-[2-(4-chlorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(l) 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(m) 3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(n) 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
(o) methyl 4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]-pyrimidin-3 -yl)ethyl]benzoate;
(p) 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
(q) 3-(2-phenylethyl)-4-hydroxy-5-pivaloyloxy-6methylpyrrolo[2,3-d]pyrimidine;
(r) 3-[2-(4-chlorophenyl)ethyl]-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo [2,3-d]pyrimidine;
(s) 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
(t) 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
(u) methyl 4-[2-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoate;
(v) 3-[2-(4-methylphenyl)ethyl]-4-hydroxypyrrolo2,3-d]pyrimidine;
(w) 3-(2-phenylethyl)-4-hydroxypyrrolo[2,3 -d]pyrimidine;
(x) 3-[2-(4-chlorophenyl)ethyl]-4-hydroxypyrrolo2,3-d]pyrimidine;
(y) 3-[2-(4-fluorophenyl)ethyl]-4-hydroxypyrrolo2,3-d]pyrimidine; and
(z) 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxypyrrolo2,3-d]pyrimidine.

EXAMPLE 8

Diethyl N-[4-55 1-(Tetrahydropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl}benzoyl]glutamate

A solution of 1.16 g of diethyl N-[4-(1-(tetrahydropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-en-2-yl)benzoyl]glutamate and 174 mg (20%) of amorphous platinum (IV) oxide in 150 ml of glacial acetic acid is hydrogenated for 10 hours at 50 psi. The reaction mixture is diluted with 50 ml of methanol and filtered through Celite. The filtrate is concentrated and diluted with ethyl acetate. The solid which forms after cooling for 15 hour is collected by filtration, washed with cold ethyl acetate and dried to give diethyl N-[4-(1-(tetrahydropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl)benzoyl]glutamate.

EXAMPLE 9

Dimethyl N-{4-0[2-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamate

A mixture of 1.1 g of dimethyl N-[4-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate in 100 mL of 50% methanol in methylene chloride and 0.8 g of 3% palladium-on-carbon is hydrogenated at 50 p.s.i. for 24 hours, filtered, and concentrated under reduced pressure. Ether is added to the residue and the solid is collected by filtration and dried to yield 0.67 g of

dimethyl N-{4-[2 -(4 -hydroxyaminopyrrolo [2,3-d]pyrimidin-3-yl)ethyl]benzoyl)-L-glutamate, mp 170°–172 ° C. ^{1}NMR (d_6-DMSO)δ1.94–2.14 (m, 2H), 2.44 (t, J=7.4 Hz, 2H), 2.93–3.02 (m, 2H), 3.57 (s, 3H), 3.63 (s, 3H), 4.40–4.70 (m, 1H), 6.71 (s, 1H), 7.29 (d, J=8.2 Hz, 2 H), 7.77 (m, 3 H), 8.66 (d, J=7.4 Hz, 1 H), 11.52 (s, 1H), 11.71 (s, 1H) .

In a similar fashion from dimethyl N-[4-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yle-thynyl)benzoyl]-L-glutamate, there is obtained according to this procedure dimethyl N-(4-[2-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)e-thyl]benzoyl)-L-glutamate, m.p. 163° C.

EXAMPLE 10

N-{4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic Acid

A mixture of 1.5 g of dimethyl N-(4-[2-(4-hydroxy6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]ben-zoyl)-L-glutamate in 10 mL of 1N sodium hydroxide is stirred at ambient temperatures for three days to form the sodium salt of N-(4-[2-(4-hydroxy-6-aminopyr-rolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl)-L-glutamic acid. This is neutralized with glacial acetic acid. The solid which forms is collected by filtration and recrys-tallized from 50% methanol in methylene chloride to give 0.8 g (67%) of N-{4-[2-(4-hydroxy-6-aminopyr-rolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl)-L-glutamic acid. ^{1}NMR (d_6-DMSO) 6 1.80–2.00 (m, 2H), 2.10–2.30 (m, 2H), 2.77–2.820 (m, 2H), 2.89–2.93 (m, 2H), 4.13–4.19 (m, 2H), 6.25 (d, J=1.3 Hz, 1H), 7.23 (d, J=8.1 Hz, 2 H), 7.69 (d, J=8.1 Hz, 2 H), 8.13 (d, J=6.7 Hz, 1 H), 10.55 (s, 1H).

EXAMPLE 11

Diethyl N-[4-{1-hydroxy-3-(4-hydroxy-6-pivaloylaminopyr-rolo[2,3-d]pyrimidin-3-yl)prop-2-yl}benzoyl]glutamate

The solution of 0.94 g of diethyl N-[4-(1-(tetrahy-dropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo-[2,3-d]pyrimidin-3-yl)prop-2-yl)benzoyl]glutamate in 40 ml of 0.1N methanolic hydrogen chloride is stirred at ambient temperatures for 2 hours. The reaction mixture is neutralized with a solution of 205 mg of sodium car-bonate in 10 ml of water and most of methanol removed by evaporation under reduced pressure. One hundred milliliters of methylene chloride are added and the solu-tion is washed twice with 20 ml of water, dried over anhydrous magnesium sulfate, and concentrated. The residue is triturated with 1:2 ethyl acetate and ether, filtered, and dried to give diethyl N-[4-{1-hydroxy-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]-pyrimidin-3-yl)prop-2-yl}benzoyl]glutamate.

EXAMPLE 12

N-[4-{1-hydroxy-3-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl}benzoyl]glutamic Acid

A solution of 0.3 g of diethyl N-[4-{1-hydroxy-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl}benzoyl]glutamate in 9 ml of 1N aqueous sodium hydroxide is stirred under nitrogen at ambient temperature for 72 hours. The reaction mixture is ren-dered slightly acidic (pH=—4) with 1N hydrochloric acid and filtered. The solid thus collected is washed with water (5 ml) and cold ethanol (5 ml) and dried to give N-[4-(1-hydroxy-3-(4-hydroxy-6-aminopyr-rolo[2,3-d]-pyrimidin-3-yl)prop-2-yl)benzoyl]glutamic acid.

Similarly from dimethyl N-(2-fluoro-4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)-ethyl]-benzoyl}-L-glutamate and dimethyl N-{3-fluoro-4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3yl)ethyl]benzoyl)-L-glutamate there are respectively obtained according to the foregoing procedure N-(2-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimi-din-3-yl)ethyl]benzoyl)-L-glutamic acid, m.p. 230° (foaming), 300° C (dec.) and N-{3-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]-benzoyl}-L-glutamic acid, m.p. >300° C. (dec.).

In an analogous fashion to the foregoing procedure, there are respectively obtained from diethyl N-{4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcabonyl}-L-glutamate, diethyl N-{5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]-pyrimi-din-3-yl)ethyl]thien-3-ylcabonyl}-L-glutamate, di-methyl N-{5-[2-(4-hydroxy-6-pivaloylaminopyr-rolo[2,3d]pyrimidin-3-yl)ethyl]fur-2-ylcabonyl}-L-glutamate, and dimethyl N-{5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcabonyl}-L-glutamate, the compounds N-{4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]-thien-2-ylcarbonyl}-L-glutamic acid, N-{5-[2-(4-hydroxy-6-aminopyrrolo[2,3d]pyrimidin-3-yl)ethyl]thi-en-3-ylcarbonyl)-L-glutamic acid, N-{5-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]fur-2-ylcar-bonyl}-L-glutamic acid, m.p. 200°–203° C., and N-{5-[2-(4-hydroxy-6-aminopyrrolo[2,3d]pyrimidin-3-yl)e-thyl]thien-2-ylcarbonyl}-L-glutamic acid, m.p. 241°–243° C.

Similarly obtained from dimethyl N-[5-(4-hydroxy6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)pentanoyl]-L-glutamate, dimethyl N-[7-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)heptanoyl]-L-glutamate, and dimethyl N-[6-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)-hexanoyl]-L-glutamate, are, respectively, N-[5-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)pentanoyl]-L-glutamic acid, N-[7-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)heptanoyl]-L-glutamic acid, and N-[6-(4-hydroxy-6-aminopyrrolo[2,3-d]-pyrimidin-3-yl)hex-anoyl]-L-glutamic acid.

EXAMPLE 13

N-{4-[2-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-yl)ethyl]-benzoyl}-L-glutamic Acid

A mixture of 0.5 g of dimethyl N-{4-[2-(4hydrox-ypyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-gluta-mate in 3 mL of 1N sodium hydroxide is stirred at ambi-ent temperatures for three days to form the sodium salt of N-{4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid. This is neutralized with hydrochloric acid. The solid which forms is col-lected by filtration and recrystallized from methanol by addition of water to give 0.35 g (75%) of N-{4-[2-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-yl)ethyl]-benzoyl}-L-glutamic acid. m.p. >230° C., ^{1}NMR (d_6-DMSO)δ1.-88–2.12 (m, 2H), 2.33 (t, J=7.3 Hz, 2H), 2.97 (m, 4H), 4.33–4.40 (m, 1H), 6.70 (d, J=1.2 Hz, 1H), 7.28 (d, J=7.0 Hz, 2 H), 7.76 (m, 3H), 8.50 (d, J=7.6 Hz, 1H), 11.48 (s, 1H), 11.67 (s, 1H), 12.40 (br, 1H) .

In a similar fashion from dimethyl N-{4-[2-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimi-din-3-yl)ethyl]benzoyl}-L-glutamate, there is obtained

according to the foregoing procedure first the sodium salt of N-{4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid which upon neutralization with glacial acetic acid yields N-{4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid, m.p. 291 ° C. ^{1}NMR (d_6-DMSO)δ2.32 (m, 4H), 2.48 (s, 3H), 2.96 (m, 4H), 4.26 (m, 1H), 6.60 (s, 1H), 7.26 (d, J=8.0 Hz, 1 H), 7.75 (d, J=7.76 Hz, 1H), 8.44 (d, J=2.96 Hz, 1H), 11.26 (s, 1H), 11.59 (s, 1H) .

By subjecting methyl 4-[2-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoate; 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-(2-phenylethyl)4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-chlorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-fluorophenyl)ethyl]4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; and methyl 4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]-pyrimidin-3-yl)ethyl]benzoate to the foregoing procedure, there are respectively obtained 4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoic acid; 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-6aminopyrrolo[2,3-d]pyrimidine; 3-(2-phenylethyl)-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine; 3-[2-(4chlorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-6aminopyrrolo[2,3-d]pyrimidine; 3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, m.p. 295°–298°; 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6aminopyrrolo[2,3-d]pyrimidine, m.p. 280°–284° C.; and 4 [2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoic acid, m.p. >300° C.

EXAMPLE 14

Representative inhibition values against CCRF-CEM 5 cell cultures for typical compounds are as follows:

Compound	IC_{50} (μg/ml)
4-[2-(4-hydroxy-6-amino-pyrrolo[2,3-d]pyrimidin-3-yl)-ethyl]benzoic acid	>20.00
N-{4-[2-(4-hydroxy-6-amino-pyrrolo[2,3-d]pyrimidin-3-yl)-ethyl]benzoyl}-L-glutamic acid	0.004
3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine	>20.00
N-{2-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid	0.008
N-{3-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid	0.019
3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine	>20.00
N-{5-[2-(4-hydroxy-6-amino-pyrrolo[2,3-d]pyrimidin-3-yl)ethyl]-thien-2-ylcarbonyl}-L-glutamic acid	0.025
N-{5-[2-(4-hydroxy-6-amino pyrrolo[2,3-d]pyrimidin-3-yl)ethyl] fur-2-ylcarbonyl}-L-glutamic acid	>20.00
N-{4-[2-(4-hydroxy-6-methyl-pyrrolo[2,3-d]pyrimidin-3-yl)ethyl]-benzoyl}-L-glutamic acid	0.0084
N-{4-[2-(4-hydroxypyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid	1.20

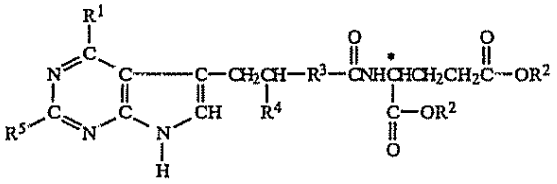
The cytotoxicity of these compounds is not reversed by the addition of hypoxanthine or AICA, suggesting they do not inhibit the purine de novo biosynthesis pathway, but is reversed by thymidine, indicating thymidylate synthetase is the main target. Cytotoxicity is also reversed by addition of leucovorin, indicating the cytotoxicity is due to antagonism of a folate-related mechanism.

In vivo activity can be seen from the following representative data for N-{4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid against the L5178Y/TK$^-$ tumor line in DBA/2 mice (female), administration being ip in a total volume of 0.5 mL daily for eight days:

	Dose %	Inhibition	Toxicity	Tumor Weight
Control	0.0	0	0/6	3606 ± 2099
Control	0.0	0	0/6	5533 ± 1234
	200.00	100	0/7	0 ± 0
	100.00	100	0/7	0 ± 0
	50.00	100	0/6	0 ± 0
	25.00	100	0/7	0 ± 0
	12.50	98	0/7	102 ± 166

What is claimed is:

1. A compound of the formula:



in which:

R^1 is —OH or —NH_2;

R^2 is hydrogen or a pharmaceutically acceptable cation:

R^3 is 1,4-phenylene unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl;

R^4 is hydrogen, or methyl;

R^5 is amino; and

the configuration about the carbon atom designated * is S.

2. A compound according to claim 1 wherein R^1 is —OH; R^3 is 1,4-phenylene, and R^4 is hydrogen.

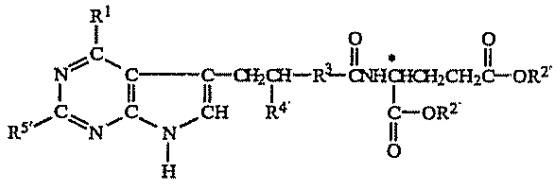
3. The compound according to claim 1 which is N-{4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid.

4. The compound according to claim 1 which is N-{4-[1-hydroxy-3-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl]benzoyl}glutamic acid.

5. The compound according to claim 1 which is N-{2-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid.

6. The compound according to claim 1 which is N-{3-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl}-L-glutamic acid.

7. A compound of the formula:



in which:

R^1 is —OH or —NH_2;

$R^{2'}$ is hydrogen, a pharmaceutically acceptable cation, or a carboxy protecting group:

R^3 is 1,4-phenylene unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl;

$R^{4'}$ is hydrogen, or methyl;

$R^{5'}$ is amino or amino substituted with an amino protecting group; and

the configuration about the carbon atom designated * is S.

* * * * *

JS 44 (Rev 12/07)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provide by local rules of court This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiatin the civil docket sheet (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM)

I. (a) PLAINTIFFS

ELI LILLY AND COMPANY
THE TRUSTEES OF PRINCETON UNIVERSITY

(b) County of Residence of First Listed Plaintiff Marion County
(EXCEPT IN U S PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Frederick L. Cottrell, III
Anne Shea Gaza, Esquire
Richards, Layton & Finger
One Rodney Square - P O Box 551
Wilmington, DE 19899
302-651-7700

DEFENDANTS

TEVA PARENTERAL MEDICINES, INC

County of Residence of First Listed Defendant
(IN U S PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.
Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

O 1 U.S Government Plaintiff
● 3 Federal Question (U S Government Not a Party)
O 2 U.S. Government Defendant
O 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	O 1	O 1	Incorporated *or* Principal Place of Business In This State	O 4	O 4
Citizen of Another State	O 2	O 2	Incorporated *and* Principal Place of Business In Another State	O 5	O 5
Citizen or Subject of a Foreign Country	O 3	O 3	Foreign Nation	O 6	O 6

IV. NATURE OF SUIT (Place an "X" in One Box Onl

CONTRACT
O 110 Insurance
O 120 Marine
O 130 Miller Act
O 140 Negotiable Instrument
O 150 Recovery of Overpayment & Enforcement of Judgment
O 151 Medicare Act
O 152 Recovery of Defaulted Student Loans (Excl Veterans)
O 153 Recovery of Overpayment of Veteran's Benefits
O 160 Stockholders' Suits
O 190 Other Contract
O 195 Contract Product Liability
O 196 Franchise

REAL PROPERTY
O 210 Land Condemnation
O 220 Foreclosure
O 230 Rent Lease & Ejectment
O 240 Torts to Land
O 245 Tort Product Liability
O 290 All Other Real Property

TORTS

PERSONAL INJURY
O 310 Airplane
O 315 Airplane Product Liability
O 320 Assault, Libel & Slander
O 330 Federal Employers' Liability
O 340 Marine
O 345 Marine Product Liability
O 350 Motor Vehicle
O 355 Motor Vehicle Product Liability
O 360 Other Personal Injury

PERSONAL INJURY
O 362 Personal Injury - Med. Malpractice
O 365 Personal Injury - Product Liability
O 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
O 370 Other Fraud
O 371 Truth in Lending
O 380 Other Personal Property Damage
O 385 Property Damage Product Liability

CIVIL RIGHTS
O 441 Voting
O 442 Employment
O 443 Housing/ Accommodations
O 444 Welfare
O 445 Amer w/Disabilities - Employment
O 446 Amer w/Disabilities - Other
O 440 Other Civil Rights

PRISONER PETITIONS
O 510 Motions to Vacate Sentence
Habeas Corpus:
O 530 General
O 535 Death Penalty
O 540 Mandamus & Other
O 550 Civil Rights
O 555 Prison Condition

FOREFEITURE/PENALTY
O 610 Agriculture
O 620 Other Food & Drug
O 625 Drug Related Seizure of Property 21 USC 881
O 630 Liquor Laws
O 640 R.R. & Truck
O 650 Airline Regs.
O 660 Occupational Safety/Health
O 690 Other

LABOR
O 710 Fair Labor Standards Act
O 720 Labor/Mgmt. Relations
O 730 Labor/Mgmt.Reporting & Disclosure Act
O 740 Railway Labor Act
O 790 Other Labor Litigation
O 791 Empl Ret. Inc Security Act

IMMIGRATION
O 462 Naturalization Application
O 463 Habeas Corpus - Alien Detainee
O 465 Other Immigration Actions

BANKRUPTCY
O 422 Appeal 28 USC 158
O 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
O 820 Copyrights
● 830 Patent
O 840 Trademark

SOCIAL SECURITY
O 861 HIA (1395ff)
O 862 Black Lung (923)
O 863 DIWC/DIWW (405(g))
O 864 SSID Title XVI
O 865 RSI (405(g))

FEDERAL TAX SUITS
O 870 Taxes (U S. Plaintiff or Defendant)
O 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
O 400 State Reapportionment
O 410 Antitrust
O 430 Banks and Banking
O 450 Commerce
O 460 Deportation
O 470 Racketeer Influenced and Corrupt Organizations
O 480 Consumer Credit
O 490 Cable/Sat TV
O 810 Selective Service
O 850 Securities/Commodities/ Exchange
O 875 Customer Challenge 12 USC 3410
O 890 Other Statutory Actions
O 891 Agricultural Acts
O 892 Economic Stabilization Act
O 893 Environmental Matters
O 894 Energy Allocation Act
O 895 Freedom of Information Act
O 900Appeal of Fee Determination Under Equal Access to Justice
O 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

● 1 Original Proceeding
O 2 Removed from State Court
O 3 Remanded from Appellate Court
O 4 Reinstated or Reopened
O5 Transferred from another district (specify)
O6 Multidistrict Litigation
O7 Judge from Magistrate Judgment
Appeal to District

Cite the U S Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**

VI. CAUSE OF ACTION

Brief description of cause: Action for infringement of U S Patent No 5,344,932 arising under 35 U S C §§271 et seq

VII. REQUESTED IN COMPLAINT:

O CHECK IF THIS IS A **CLASS ACTION** **DEMAND $** CHECK YES only if demanded in complaint:

JURY DEMAND: O Yes ●No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE DOCKET NUMBER:

DATE June 5, 2008 SIGNATURE OF ATTORNEY OF RECORD

Anne Shea Gaza

FOR OFFICE USE ONLY

RECEIPT # AMOUNT APPLYING IFP JUDGE MAG JUDGE

RLF1-3289680-1

JS 44 Reverse (Rev 12/07)

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title

(b) County of Residence For each civil case filed, except U S plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing In U S plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved)

(c) Attorneys Enter the firm name, address, telephone number, and attorney of record If there are several attorneys, list them on an attachment, noting in this section "(see attachment)"

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F R C P , which requires that jurisdictions be shown in pleadings Place an "X" in one of the boxes If there is more than one basis of jurisdiction, precedence is given in the order shown below

United States plaintiff (1) Jurisdiction based on 28 U S C 1345 and 1348 Suits by agencies and officers of the United States are

included here United States defendant (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in

this box

Federal question (3) This refers to suits under 28 U S C 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States In cases where the U S is a party, the U S plaintiff or defendant code takes precedence, and box 1 or 2 should be marked

Diversity of citizenship (4) This refers to suits under 28 U S C 1332, where parties are citizens of different states When Box 4 is checked, the citizenship of the different parties must be checked (See Section III below; federal question actions take precedence over diversity cases)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above Mark this section for each principal party

IV. Nature of Suit. Place an "X" in the appropriate box If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit If the cause fits more than one nature of suit, select the most definitive

V. Origin. Place an "X" in one of the seven boxes

Original Proceedings (1) Cases which originate in the United States district courts

Removed from State Court (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U S C , Section 1441 When the petition for removal is granted, check this box

Remanded from Appellate Court (3) Check this box for cases remanded to the district court for further action Use the date of remand as

the filing date Reinstated or Reopened (4) Check this box for cases reinstated or reopened in the district court Use the reopening date as

the filing date

Transferred from Another District (5) For cases transferred under Title 28 U S C Section 1404(a) Do not use this for within district transfers or multidistrict litigation transfers

Multidistrict Litigation (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U S C Section 1407 When this box is checked, do not check (5) above

Appeal to District Judge from Magistrate Judgment (7) Check this box for an appeal from a magistrate judge's decision

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause **Do not cite jurisdictional statutes unless diversity.** Example: U S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service

VII. Requested in Complaint. Class Action Place an "X" in this box if you are filing a class action under Rule 23, F R Cv P

Demand In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a

preliminary injunction Jury Demand Check the appropriate box to indicate whether or not a jury is being demanded

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases if any If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases

Date and Attorney Signature. Date and sign the civil cover sheet